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News & Highlights

First CRISPR-based Therapy Poised to Reach Patients

Jennifer Welsh

Senior Technology Writer

Ten years after the discovery of clustered regularly interspaced short palindromic repeats (CRISPR), the first gene-editing therapy is expected to soon receive US Food and Drug Administration (FDA) approval for commercial use in patients. Also expected? An enormous price tag.

Developed jointly by Vertex Pharmaceuticals (Boston, MA, USA) and CRISPR Therapeutics (Zug, Switzerland), exagamglogene autotemcel, or "exa-cel," treats two life-threatening genetic blood disorders: sickle cell disease (SCD) and transfusion-dependent β-thalassemia (TDT) [1]. The FDA accepted the exa-cel biologics license application (BLA) for SCD in June 2023, with approval expected by 8 December 2023; the BLA filing for TDT is expected by 30 March 2024 [2]. Approval for both indications by the European Medicines Agency is also expected by the end of 2023 [3].

"I am very confident that [exa-cel] will be approved," said Matthew Porteus, professor of pediatrics at Stanford Medicine, Palo Alto, and a pediatric hematologist at Stanford Medicine Children's Health in Stanford, CA, USA. As a scientific founder of CRISPR Therapeutics, Porteus holds equity in the company but serves no advisory role. "When approved, it will not only be the first CRISPR-based drug approved by the FDA, but also the first gene editing therapy."

CRISPR is a set of molecular mechanisms bacteria use to identify and destroy viral genes [4]. In research that won 2020's Nobel Prize for chemistry [5], scientists discovered they could use CRISPR to home in on a specific spot in a deoxyribonucleic acid (DNA) strand and cut it, swapping in a new nucleotide or gene, or deleting sections of the existing gene [1]. The efficient gene editing enabled by CRISPR's ease of use, speed, specificity, and precision have led to it becoming an essential tool in biological laboratories worldwide [4]. Since its discovery, scientists have applied CRISPR to myriad areas of research, from basic science discovery to enhancing important crops [6] and livestock and treating genetic diseases and cancers in humans.

As the world's most common monogenic (single gene) diseases in humans, the beta hemoglobinopathies make natural targets for gene-based therapy. Both SCD and TDT are caused by mutations in the hemoglobin beta subunit gene (HBB). Annually, an estimated 300 000 and 60 000 people, respectively, receive diagnoses of SCD and TDT worldwide [1]. "Both of these diseases are associated with shortened lifespan, high demands for complex medical care, and lots of complications," said Alexis Thompson, chief of hematology and professor of pediatrics at the University of Pennsylvania Perelman School of Medicine in Philadelphia, PA, USA, and an investigator in clinical trials of novel therapies—including exa-cel—for patients with beta hemoglobinopathies.

The defective hemoglobin produced by mutated HBB creates dysfunctional red blood cells (RBCs). People with TDT do not have enough healthy RBCs to carry oxygen around the body, resulting in severe, debilitating anemia [8]. "Through their entire lives, these patients need blood transfusions every two to four weeks," Thompson said. Such repeated blood transfusions can lead to iron toxicity among many other health issues. People with SCD have deformed, sickle-shaped RBCs, which can clog blood vessels when they burst and clump (Fig. 1) [9]. "Before the age of two, infants with sickle cell disease begin having painful episodes," Thompson said. "They then go on to have even more frequent and severe complications." Standard treatment for SCD includes medications that can lessen, but not prevent, episodes of pain and other complications [8]. For decades, a bone marrow transplant (BMT) from an antigenically matched donor has been the only potentially curative therapy for patients with SCD and TDT [9]. But such donors are only available in less than 20% of cases [1], which is why having an effective alternative is exciting, Thompson said. "Gene therapy gives an option to the many patients who do not have matched donors."

The CRISPR gene editing in exa-cel therapy induces an effect that mimics the natural protective effect of fetal hemoglobin. Children with SCD or TDT often do not have symptoms in the first year of life because their RBCs contain high levels of fetal hemoglobin [1], which subside with the activation of gamma-globin gene repressor BCL11A that normally occurs by the age of two years. Exa-cel uses CRISPR/Cas9 and a single-guide ribonucleic acid (RNA) molecule to introduce a DNA "typo," a gene deletion that deactivates the repressor, thereby allowing the patient's hematopoietic stem and progenitor cells (HSPCs) to produce RBCs with fetal hemoglobin (Fig. 2) [1]. The increased levels of these RBCs compensate for the ones with defective hemoglobin, which alleviates the symptoms [8].

Importantly, the therapy involves an *ex-vivo* process in which the patient's HSPCs are removed, isolated, and then gene edited

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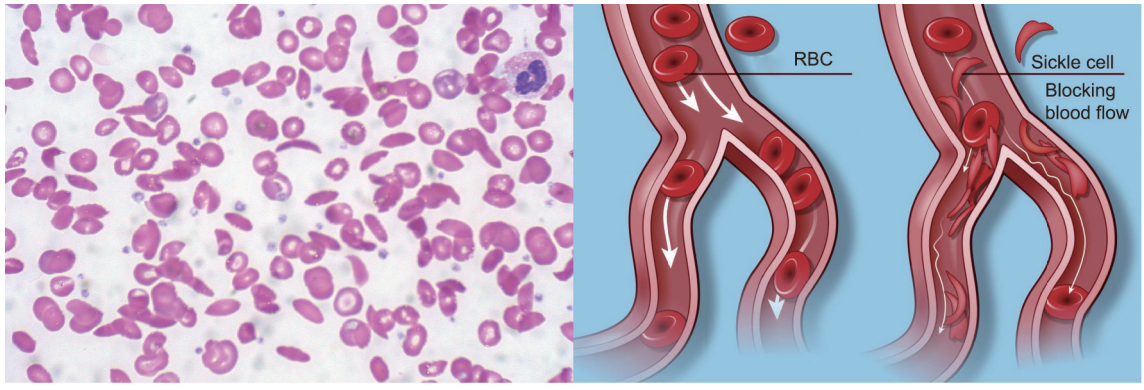

Fig. 1. (a) People with SCD have deformed, sickle-shaped RBCs caused by a mutation in the HBB. (b) When the defective RBCs burst and clump, they clog blood vessels causing painful vaso-occlusive events called crises. Lifetime treatment for these painful episodes and other complications can amount to millions of dollars of healthcare costs for individual patients. Credits: (a) Ed Uthman/Flickr (CC BY 2.0); (b) Darryl Leja, NHGRI (CC BY 2.0).

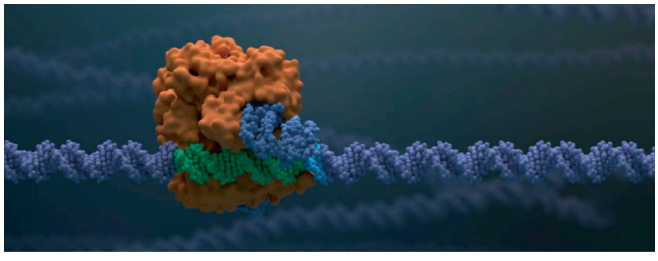

Fig. 2. In exa-cel gene editing, CRISPR/Cas9 (orange) and a guide RNA (blue) work together to precisely introduce breaks (light blue) in the DNA (green) of a repressor gene, introducing a "typo" that turns the repressor off and allows the production of fetal hemoglobin. The resulting RBCs with fetal hemoglobin compensate for RBCs with defective hemoglobin, alleviating the symptoms of both SCT and TDT. Credit: Vertex Pharmaceuticals (public domain).

in a laboratory (Fig. 3) [9]. The patient's bone marrow is then ablated using chemotherapy, as in a typical BMT, and the cells with the CRISPR-edited gene are infused back into the patient to engraft [8]. In a matter of weeks, these multiplying cells begin making RBCs with fetal hemoglobin [1].

"This is not just a proof of concept—this is a really important therapy for patients with SCD," said Porteus. "It is transformative and changes patient lives." That impact is clear from the clinical trial data [10], which showed that exa-cel helped 42 of 44 TDT patients be transfusion-free at 12.3 months, down from an average 36 transfusions annually; the two patients still receiving transfusions needed 75% and 89% less blood. Whereas the 31 patients with SCD had an average of almost four crises annually before treatment [8], all were free of vaso-occlusive disease at 9.6 months post-treatment. On average, fetal hemoglobin comprised about 40% of the patients' hemoglobin [8]. "It is very exciting to see Nobel Prize-winning CRISPR work translated into treatment in this clinical space," Thompson said. "These are remarkable research studies."

Two patients experienced severe adverse events, including low platelet count and a buildup of white blood cells that can damage organs [8]. Other adverse events included pneumonia and sepsis due to low white blood cell count [1], complications expected with chemotherapy ablation of the bone marrow [11]. But none of the patients died or dropped out of the study [10].

It is unknown how long the benefits of exa-cel will last. The trials include following the patients for at least 15 years [8], but patients receiving similar genetic therapies have remained disease-free for more than a decade, Porteus said. "We cannot know that in five or ten years, for some reason we do not now understand, all of a sudden the genetically engineered stem cells all die off," Porteus said. "But that has not happened in other BMT programs."

While the positive data from the exa-cel clinical trials provide a high benchmark for competitors developing other gene-based therapies [11], many experts think there is ample opportunity for multiple approaches. "For many years, the complexity of manufacturing is going to support several drugs to meet the demand of patients for these tailored treatments," Porteus said.

One such competitor, a gene-based therapy to treat TDT, was approved by the FDA in August 2022 [12]. Betibeglogene autotemcel (beti-cel), from Bluebird Bio (Cambridge, MA, USA), uses a lentivirus vector to add functional copies of a modified form of the β-globin gene to HSPCs in an *ex-vivo* procedure like that used with exa-cel. Instead of changing the genetic code (gene editing), the viral vector adds a new gene into the cells (a gene therapy, sometimes called gene addition). Bluebird's competitor for SCD, lovotibeglogene autotemcel (lovo-cel), another lentivirus vector gene therapy, is currently in BLA review at the FDA, with an expected decision on 20 December 2023 [13]. Several other potential competitors in early-to-mid-stage clinical trials that also use CRISPR gene editing are EDIT-301 from Editas Medicine (Cambridge, MA, USA) [14] and BEAM-101 from Beam Therapeutics (Cambridge, MA, USA) [15]; another approach using RNA silencing of BCL11A is being developed by a team at Boston Children's Hospital (Boston, MA, USA) [16]. "I personally do not have enough confidence to say that one of these will be superior to the others," Thompson said. "Biologically, these are different approaches, targeting different genes—each may have some unique consequences, but potentially similar clinical benefit."

Perhaps the biggest—and most impactful—question about these new therapies is how much they will cost. Gene-based therapies have regularly set records for the most expensive drugs on the market. The current highest-priced drug is a gene therapy for hemophilia B, etranacogene dezaparvovec-drlb, brand name Hemegenix, jointly developed by CSL Behring (King of Prussia, PA, USA) and uniQure (Lexington, MA, USA). FDA-approved in November 2022, Hemegenix costs 3.5 million USD [7]. Bluebird's beti-cel, brand name Zynteglo, costs 2.8 million USD [7]. FDA-approved in June 2023, delandistrogene moxeparvovec, brand name Elevidys, a gene therapy developed by Sarepta (Cambridge, MA, USA) for Duchenne muscular dystrophy, costs 3.2 million USD [18].

Stakeholders say these drugs are worth the high prices because the apparent cures they produce cut a lifetime of medical costs. For example, one 2023 study calculated that a cure that costs up to 2 million USD would be a cost-effective treatment for patients with

Fig. 3. As shown in this schematic of the clinical trial design, exa-cel therapy, which can take up to a year to complete, involves an *ex-vivo* procedure where the patient's HSPCs are removed and sent to a laboratory for gene editing using CRISPR/Cas9 and a single-guide RNA molecule to introduce a deletion in the BCL11A repressor gene. After the patient's bone marrow has been ablated by chemotherapy, as in a typical BMT, the edited cells are infused back into the patient. In a matter of weeks, the engrafted cells multiply and begin making RBCs with fetal hemoglobin. Credit: Vertex Pharmaceuticals (public domain).

severe SCD [19]. Other estimates of lifetime costs for the treatment of a single patient with severe SCD in the United States run between 4 million and 6 million USD [20]. Given the price tags of other gene therapies, exa-cel will likely cost more than 2 million USD [21], perhaps as much or more than 3 million USD, Porteus said. As of September 2023, Vertex had yet to announce a price.

While they appear to be effective therapies, exa-cel and all other gene-based therapies in late-stage clinical development require chemotherapy ablation of the bone marrow, a time-intensive, high-risk, unpleasant, and expensive procedure that can result in infertility and other complications. Patients must put their lives on hold for months to undergo the procedure at a specialized facility [17]. In addition, the transplantation and engraftment process that follows ablation may prematurely age the gene-edited stem cells, Porteus said, which could potentially increase the risk of cancer decades later.

'Cancer is also a risk of the genetic translocations or rearrangements caused by CRISPR/Cas9 gene editing. The guide RNA may also introduce off-target editing or indels (insertions and deletions) in other areas of the genome. By carefully selecting the guide RNA used, researchers have tried to predict and mitigate off-target effects, and the risk is much smaller with CRISPR than with other gene therapy tools [8]. "In lentiviral gene therapy, every insertion is—by definition—an off-target mutation because there is no target," Porteus said. "In some of the lentiviral gene therapy trials, there has been some cancer risk because the insertion activates a cancer gene." To date, no off-target effects, translocations, or rearrangements—or cancers—have been reported in the exa-cel trials [8].

Aside from their budget-busting prices, a challenge remains to ensure these therapies, once approved, are widely available to patients who might benefit. Ramping up the complex manufacturing involved is not trivial, Porteus said. According to Vertex, exa-cel's planned commercial launch will include 50 and 25 authorized treatment centers, respectively, in the United States and Europe; the company has already prepared a supply chain and built manufacturing capacity [11]. Initial use of the treatment will likely be limited to the severely ill, with around 25 000 qualifying patients in the United States [17].

"The real problem is what we do about the rest of the world," Thompson said. "Gene-based therapy in its current state will continue to be expensive and mostly out of reach for many parts of the globe." More than 60% of people with SCD live in sub-Saharan Africa, where there are only three BMT centers [21]. Massive investment in clinical infrastructure would be needed to offer current gene therapies there and elsewhere in the developing world [20].

Ridding gene-based therapy of the ablation and transplant parts could make it more accessible but would require changing the gene editing involved to an *in-vivo* procedure, for which new ways to deliver genes and gene editing components are an active area of investigation. Not having an effective and safe way to perform gene editing *in-vivo* is one of the biggest hurdles to developing CRISPR therapies, and greatly limits the types of diseases that might be treated by gene editing [22].

One new approach that appears promising for getting CRISPR into a precisely targeted population of cells *in-vivo* is a tool borrowed from nature and honed using artificial intelligence. In a 2023 report published in *Nature* [23], researchers described a naturally occurring "bio-needle" mechanism adapted from the phage viruses that ubiquitously infect bacteria. These modifiable bio-needles have the potential to facilitate *in-vivo* gene editing, demonstrating precise and efficient delivery of CRISPR components into cultured human cells and targeted cells in the brains of live mice. But these innovations are in their infancy. "It will take some time to put all the moving parts together for these [*in-vivo*] delivery mechanisms and strategies," Porteus said. "Just like it took a lot of people a lot of years to get the *ex-vivo* systems to work."

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